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**THE TRAJECTORY OF RADIOGRAPHIC CHANGE OVER A DECADE:
PROGRESSION AS MEASURED BY THE PsA-MODIFIED SHARP VAN DER
HEIDJE SCORE (mSvdHS) SLOWS AMONGST PATIENTS WITH PSORIATIC
ARTHRITIS TREATED WITH ANTI-TNF**

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Key Words

Psoriatic arthritis, anti-tumour necrosis factor (anti-TNF), disease modifying anti-rheumatic drugs (csDMARD), radiographic progression

Abstract

Objectives: To describe the trajectory of radiographic progression amongst patients with psoriatic arthritis (PsA) who transitioned from conventional synthetic disease modifying drugs (csDMARDs) to anti-tumour necrosis factor alpha inhibitors (anti-TNF) in routine care.

Methods: A retrospective sample of patients with PsA (CASPAR criteria) was taken from the Bath longitudinal cohort. All patients had radiographs of the hands and feet taken: five years before [T₀], at the time of [T₁] and five years post [T₂] commencing anti-TNF treatment. Radiographs were scored blinded using the PsA-modified Sharp-van der Heijde score (mSvdHS) and for osteoproliferation (PARS) by AA, AA and WT. This sample size was calculated to ensure 90% power to determine the smallest detectable difference of the mSvdHS to a 5% significance level. Cumulative probability plots were used to determine the probability of radiographic progression pre- (T₀-T₁) and post- (T₁-T₂) anti-TNF treatment.

Results: Eighty four radiographs from twenty eight patients were selected for inclusion. The median (IQR) disease duration at baseline (T₀) was 8.5 (0-19.5) years. The interval between T₀-T₁ and T₁-T₂ was 4.2 years (3.34-6.65) and 4.9 years (4.25-5.87) respectively. The median mSvdHS at baseline (T₀) was 8.5 (IQR 1.75-27.5). The median (IQR) rate of change in mSvdHS per year reduced after commencing anti-TNF from 2.1 (0.88-3.92) between T₀-T₁ to 1.0 (IQR 0.05-2.35) between T₁-T₂ (p=0.012).

Conclusion: The trajectory of damage accumulation over a 10 year period in this observational clinical cohort is low overall. The rate of radiographic damage as measured by the mSvdHS slows following commencement of anti-TNF.

(249/250 words)

Key message: Radiographic progression slows in patients escalated from csDMARD to anti-TNF therapy in this long-term study. (15/15 words)

Background:

Plain radiography and the quantification of radiographic damage is an important outcome in psoriatic arthritis (PsA) from the patient and clinician perspective. Patients rank the prevention of damage as a high priority from treatment¹. Clinicians recognise that the tight control of disease with early intervention and a treat to target approach in rheumatoid arthritis has led to less damage accumulation and improved physical function in established disease². Data are emerging that a similar approach may improve outcome in PsA^{3,4}.

Previous perceptions of PsA as a relatively mild arthropathy have been succeeded by observational studies describing the prevalence and progression of radiographic damage over time. In an observational study of 129 patients with early PsA, 27% were found to have erosive disease at baseline and 47% had erosive disease at 2 years of follow-up⁵. In a cohort of 71 patients with no erosive disease at baseline, 45% developed erosions over an average follow-up period of 8 years⁶.

Whilst the slowing of long-term radiographic progression with anti-TNF treatment has been demonstrated in rheumatoid arthritis and in randomised clinical trials in PsA, there is little long term follow-up data from observational PsA cohorts using formal validation scoring systems such as the modified Sharp/van der Heijde score (mSvdHS)^{4,7,8}. Real world evidence is especially important in the field of PsA because the disease phenotype included in drug development trials are increasingly homogenous, representing predominantly polyarticular disease and under representing the oligo and monoarticular phenotypes⁹. Radiographic progression can be slow in PsA and the duration of randomised controlled trials (RCT) short, even in the extension studies; therefore there is a lack of meaningful long term follow up data in what is a lifelong disease.

We aimed to quantify the rate of radiographic progression amongst patients with PsA who transitioned from conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) to anti-tumour necrosis factor alpha (anti-TNF) therapy in routine care.

Materials and Methods:

Cohort selection

A retrospective convenience sample of 28 patients fulfilling the CASPAR criteria for PsA was taken from the Bath longitudinal cohort. Patients have clinical, patient reported and radiographic assessments as part of routine care. All patients at entry to the cohort have baseline hand and feet radiographs. All patients requiring biologic disease modifying anti-rheumatic drugs (bDMARD) have the same data collected as part of a protocol at every visit, including radiographs every two years. Baseline demographics and measures of disease activity at commencement of anti-TNF therapy and at follow-up, including tender joint count (TJC), swollen joint count (SJC), psoriasis area and severity index (PASI), Stanford Health Assessment Questionnaire Disability Index (HAQ) scores and C-reactive protein (CRP) are reported using descriptive statistics. We included all patients who had antero-posterior radiographs of the hands and feet taken at three time points; five years before [T₀], at the time of [T₁] and five years after [T₂] commencing anti-TNF treatment. This sample size was calculated to ensure 90% power to determine the smallest detectable difference of the mSvdHS (6.25 units) to a 5% significance level.

Radiographic Scoring methods

Radiographs were scored for erosions and joint space narrowing by three assessors (AA, AA and WT) using the modified Sharp/van der Heijde score (mSvdHS), which has been found to be the method that is most sensitive to change in PsA. Proliferation was also scored using the Psoriatic Arthritis Ratingen Score (PARS) method¹⁰. The technical details on radiograph acquisition and viewing have been previously reported¹¹. The assessors were blinded to patient identifiers, demographics, treatment and chronological order of the radiographs. Reliability was assessed using inter-class correlation coefficient (ICC). Inter-rater reliability was assessed using a sample of nine sets of radiographs scored by all three assessors and intra-rater reliability was assessed with individual assessors scoring the same nine radiographs three weeks after the initial inter-rater reliability exercise. The rate of radiographic progression (units per year) was calculated for the individual components of radiographic damage by dividing the change of the individual scores

over the duration of time between the radiographs at T_0 - T_1 and T_1 - T_2 for each patient.

Statistical analysis

All statistical analysis was performed using SPSS-23 (IBM Corp.). Inter-rater reliability was assessed using ICC. The significance of changes in clinical outcomes between time points was assessed using the Wilcoxon Signed-Rank test. Cumulative probability plots were used to illustrate radiographic progression pre- (T_0 to T_1) and post- (T_1 to T_2) anti-TNF treatment. The two-sample Kolmogorov-Smirnov test (K-S test) was used to determine if there was a significant change in the rate of progression following the commencement of anti-TNF therapy.

Ethics

This study has been conducted according to the principles in the Declaration of Helsinki and was approved by the Bath Research Ethics Committee. Informed written consent was obtained from all participants.

Results:

Twenty eight patients were identified for inclusion: 15 were male, the mean (\pm SD) age was 61 years (\pm 13.4) and median (IQR) disease duration at T_0 was 8.5 years (0.00-19.50). The median (IQR) study follow up period was 9.5 years (8.00-12.00). Inter-rater and intra-rater ICCs were >0.9 for the total mSvdHS and its sub-scores. Clinical outcomes at initiation of anti-TNF (T_1) are reported in Table 1.

Clinical Outcomes $T_1 - T_2$

The median (IQR) TJC, SJC, PASI and HAQ showed statistically significant improvements between T_1 to T_2 as assessed by the Wilcoxon signed-rank test. The median (IQR) TJC improved from 23 (13.5-34.0) to 6 (0.5-17.0; $p<0.0001$), the median (IQR) SJC improved from 7 (4.0-10.8) to 0 (0.0-3.5; $p<0.0001$), the median PASI improved from 0.8 (0.30-1.85) to 0.3 (0.00-0.70; $p=0.03$) and the median HAQ improved from 1.3 (0.94-2.09) to 1.1 (0.25-1.84; $p=0.01$).

Radiographic progression prior to anti-TNF ($T_0 - T_1$)

Radiographic progression on csDMARDs ($T_0 - T_1$) occurred in 89% (n=25) of patients, with progression in erosions and joint space narrowing occurring in 61% (n=17) and 86% (n=24) of patients respectively. The median mSvdHS at T_0 was 8.5 (IQR 1.75-30.50). The median scores for erosions and joint space narrowing were 1.5 (IQR 0.00-11.50) and 4.5 (IQR 1.00-15.00) respectively. The median (IQR) rate of progression in mSvdHS, erosion score and joint space narrowing score per year was 2.1 (0.88-3.93), 0.4 (0.00-1.91), and 1.4 (0.68-2.30) respectively.

Radiographic progression following anti-TNF treatment ($T_1 - T_2$)

64% of patients continued to progress radiographically following anti-TNF treatment, with 32% developing progressive erosive disease and 61% developing progressive joint space narrowing. The median (IQR) rate of change in mSvdHS per year improved to 1.0 (0.05-2.35) units/year on anti-TNF ($p=0.01$) (Figure 1). The median (IQR) rate of change of erosions improved to 0.0 units/year (0.00-0.81) and the median rate of joint space narrowing improved to 0.7 (0.05-1.81) but these values did not reach statistical significance.

Rate of progression of proliferative change pre and post anti-TNF treatment ($T_1 - T_2$)

The median (IQR) rate of proliferation numerically reduced from 0.38 units/year (-0.30-1.64) to 0.00 units/year (-0.25-0.79) post initiation of anti-TNF, but the 2 sample KS test shows no significant difference between the two groups ($p=0.346$); figure 2.

Discussion:

This study demonstrates evidence of reduced rate of radiographic progression as measured by the mSvdHS amongst patients commenced on anti-TNF therapy in an observational clinical cohort of patients with PsA.

The effect of anti-TNF on radiographic progression in PsA was first reported in a placebo-controlled RCT involving etanercept, in which the modified Sharp Score (mTSS) was used to score radiographs after the initial 24 week blinded stage and after the 48 week extension. Radiographic progression was inhibited at 12 months in the etanercept group (0.03 units) compared to a deterioration in the placebo group

(1.00 unit; $p=0.0001$)¹². Subsequent placebo-controlled RCTs involving infliximab, adalimumab, golimumab, certolizumab, ustekinumab and secukinumab, have also demonstrated an improvement in the rate of radiographic progression in the first 24 weeks of treatment, with a higher proportion of non-progressors in the bDMARD arms^{7,13,14,15,16,17}. More recently, the GO-REVEAL study has published its five year follow up data suggesting that reduction in radiographic progression is preserved through five years of treatment with golimumab¹⁸.

Ravindran *et al* reported progression of damage amongst 139 patients over a five year period using the modified Sharp Score (mSS). The study demonstrated the ability of the mSS to detect correlations between damage and physical function measured with the HAQ at baseline ($r=0.29$) and follow-up ($r=0.48$)¹⁹. A report from the Swedish early PsA registry evaluated progression of 72 patients with early PsA over the first five years of disease and noted slow rates of progression²⁰.

To our knowledge our study is the first to describe the rate of radiographic progression in a group of patients in the years leading up to and following the commencement of an anti-TNF therapy, over a ten year period.

The rate of mSvdHS progression reported in our study provides an estimate of radiographic progression over a decade of treatment in the modern era of higher dose csDMARD use and widespread adoption of bDMARD use. The overall rate of mSvdHS progression in our cohort prior to the commencement of anti-TNF therapy was low, but certainly higher than rates of progression reported in the placebo-controlled RCTs of patients with PsA, perhaps reflecting the clinical-practice complexity of a treat-to-target approach in a real-world clinical cohort with comorbidities and relative contraindications to a strict treat-to-target approach²¹.

The participants included in this study are those with active peripheral joint disease requiring bDMARD treatment, as evidenced by the median TJC, SJC and CRP of the cohort at the time of anti-TNF commencement (Table 1). However the selection of patients with a long period of treatment with csDMARDs prior to commencement of anti-TNF is a potential source of bias, as this may represent a cohort of patients with a milder disease course, in addition to patients in whom escalating to anti-TNF was

not undertaken for clinical reasons or patient preference. Conversely, it is also worth noting that by excluding patients who had incomplete sets of radiographs at the three time points, there is the potential for selection bias towards a population of more patients who may have more active disease. These caveats are a reflection of the heterogeneity of an observational clinical cohort.

We have also demonstrated a slowing of radiographic progression as measured by the mSvdHS in a cohort of PsA patients with high disease activity at the time of anti-TNF commencement, from a median mSvdHS of 2.1 to 1.0 units/year following commencement of anti-TNF treatment. This mirrored the improvements in clinical outcomes such as tender joint count, swollen joint count, PASI, and HAQ, and likely represents improvement in disease activity rather than a drug-specific effect. We demonstrate a numerical reduction in the rate of individual features of radiographic damage, but this was not statistically significant. This may be a reflection of the small sample size of our cohort, chronological blinding in radiograph scoring, or the influence of the natural history of disease of the disease over time.

The main consideration when interpreting the results of our study is the relatively small cohort size, which does not allow for a meaningful sub-group analysis to look at relative progressors versus non-progressors as separate populations. In our study, progression in joint space narrowing was responsible for a significant proportion of radiographic progression post anti-TNF, which is important to note given the lack of specificity of joint space narrowing as a radiographic outcome in PsA. The strengths of our study include the pre-determined sample size, long follow-up period, good inter-rater reliability, and formal blinded radiographic scoring.

Conclusions

We report an estimate of radiographic progression in PsA over a ten year period amongst patients with more aggressive disease who have required anti-TNF treatment as part of routine care. The trajectory of damage accumulation is low overall and the rate of progression in mSvdHS slows amongst patients commenced on anti-TNF in this clinical-practice cohort.

(Word count: 2618/3500 – not including abstract/table/graph)

Population characteristics at commencement of anti-TNF (n=28)

Baseline Demographics: Mean (\pm SD) or Median (IQR)

Sex:	Male 54 % (15)	
	Female 46% (13)	
Age:	61 years (\pm 13.45)	
Disease duration at T ₀ :	8.5 years	(0.00-19.50)
Total disease duration:	18 years	(9.25-29.50)
Duration of anti TNF treatment:	5.0 years	(4.00-6.00)
Total study follow-up:	9.5 years	(8.00-12.00)

Anti-TNF Medication: n (%)

Adalimumab	12 (43)
Etanercept	13 (46)
Golimumab	3 (11)

Clinical assessment at commencement of anti-TNF: median (IQR)

Tender joint count:	23.0	(13.50-34.00)
Swollen joint count:	7.0	(4.00-10.80)
PASI:	0.8	(0.30-1.85)
HAQ:	1.3	(0.94-2.09)
CRP:	10.0	(4.25-17.75)

Radiographic assessment at commencement of anti-TNF: median (IQR)

mSvdHS	17.50	(10.25-35.75)
Rate of Erosions	0.42	(0.00-1.91)
Rate of Joint Space Narrowing	1.43	(0.68-2.29)
Rate of mSvdHS	2.09	(0.88-3.92)

Table 1: Population characteristics at baseline.

Key: TNF = tumour necrosis factor; SD = standard deviation; IQR = inter-quartile range; PASI = psoriasis activity severity index; HAQ = health assessment questionnaire; mSvdHS = modified Sharp-van der Heijde score.

Footnote: mean (standard deviation) and median (interquartile ranges have been used throughout as appropriate.

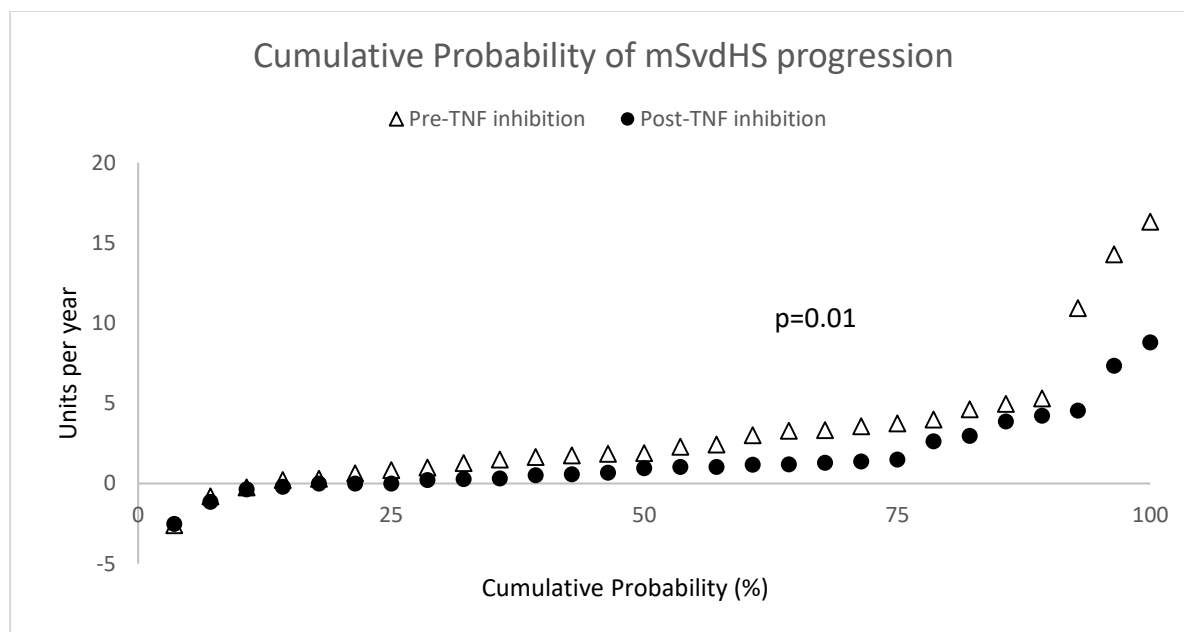


Figure 1: Cumulative probability plot demonstrating an increased rate of radiographic progression as calculated by median mSvdHS score in patients on csDMARDs compared with anti-TNF treatment.

Key: mSvdHS = modified Sharp-van der Heijde score; TNF = tumour necrosis factor.

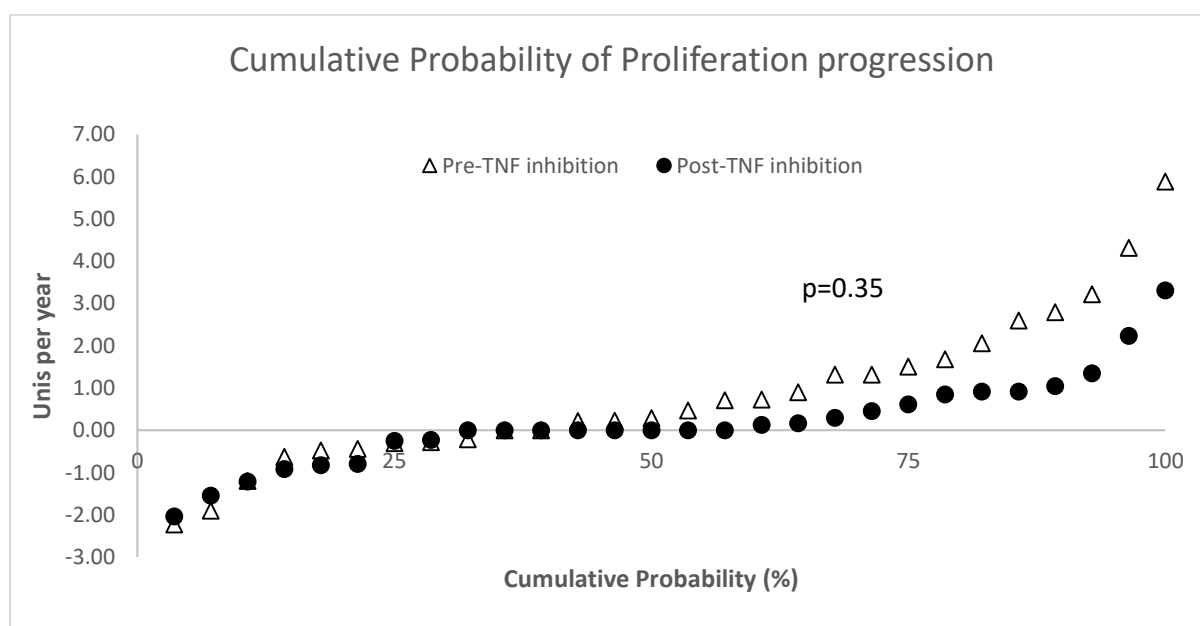


Figure 2: Cumulative probability plot demonstrating changes in rate of progression of proliferation pre and post TNF inhibition.

Key: TNF = tumour necrosis factor.

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